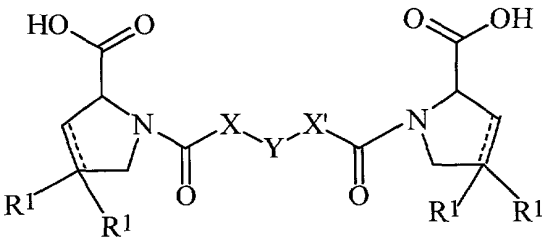
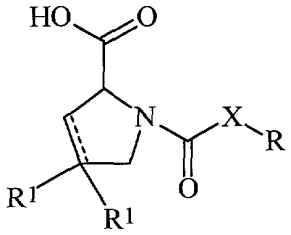
CLAIMS:

1. Agent for the depletion of an unwanted protein population from the plasma of a subject, which agent comprises a plurality of ligands covalently co-linked so as to form a complex with a plurality of the proteins in the presence thereof, wherein at least two of the ligands are the same or different and are capable of being bound by ligand binding sites present on the proteins, wherein the agent is a non-proteinaceous agent other than a D-proline of the formula



I-A

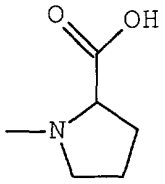
or



I-B

wherein

R is



the group ;

R^1 is hydrogen or halogen;

X is- $(CH_2)_n$-; -$CH(R^2)(CH_2)_n$-; -$CH_2O(CH_2)_n$-; -CH_2NH-; benzyl, -$C(R^2)$=CH-; -$CH_2CH(OH)$-; or thiazol-2,5-diyl;

Y is –S-S-; -$(CH_2)_n$-; -O-; -NH-; -$N(R^2)$-; -CH=CH-; -NHC(O)NH-;- $N(R^2)C(O)N(R^2)$-; -$N[CH_2C_6H_3(OCH_3)_2]$-; -$N(CH_2C_6H_5)$-; -$N(CH_2C_6H_5)C(O)N(CH_2C_6H_5)$-; -N(alkoxyalkyl)-;

N(cycloalkyl-methyl)-; 2,6-pyridyl; 2,5-furanyl; 2,5-thienyl; 1,2-cyclohexyl; 1,3-cyclohexyl; 1,4-
cyclohexyl; 1,2-naphthyl; 1,4-naphthyl; 1,5-naphthyl; 1,6-naphthyl;
biphenylen; or 1,2-phenylen,1,3-phenylen and 1,4-phenylen, wherein the phenylen groups are optionally substituted by 1 – 4 substituents, selected from halogen, lower alkyl, lower alkoxy, hydroxy, carboxy, -COO-lower alkyl, nitrilo, 5-tetrazol, (2-carboxylic acid pyrrolidin-1-yl)-2-oxo-ethoxy, N-
hydroxycarbamimidoyl, 5-oxo[1,2,4]oxadiazolyl, 2-oxo-
[1,2,3,5]oxathiadiazolyl, 5-thioxo[1,2,4]oxadiazolyl and 5-tert-butylsulfanyl-[1,2,4]oxadiazolyl;

X' is $-(CH_2)_n$-; $-(CH_2)_nCH(R^2)$-; $-(CH_2)_nOCH_2$-; $-NHCH_2$-;
benzyl, $-CH=C(R^2)$-; $-CH(OH)CH_2$; or thiazol-2,5-diyl;

R^2 is lower alkyl, lower alkoxy or benzyl and

n is 0-3,

or a pharmaceutically acceptable salt or mono- or diester thereof.

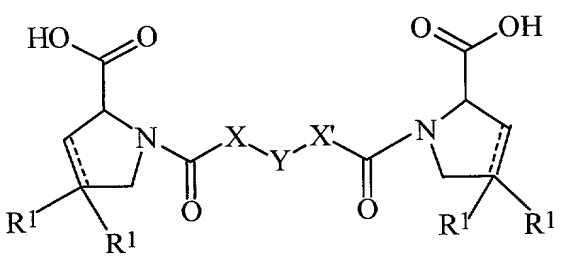
2. Agent according to claim 1, wherein the ligands are covalently co-linked by a linker.

3. Agent according to claim 2, wherein the linker comprises a linear or branched hydrocarbylene in which one or more of the carbon atoms thereof is optionally substituted by a heteroatom.

4. Agent according to claim 1, which has two ligands.

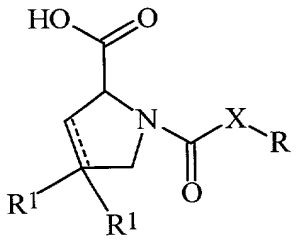
5. Agent for the depletion of an unwanted protein population from the plasma of a subject, which agent has the general structure Ligand-linker-Ligand and is capable of forming a complex with a plurality of the proteins in the presence thereof, wherein the ligands are the same or different and are capable of being bound by ligand binding sites

present on the proteins, wherein the agent is a non-proteinaceous agent other than a D-proline of the formula



I-A

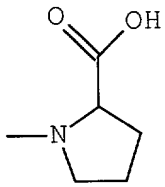
or



I-B

wherein

R is



the group ;

R^1 is hydrogen or halogen;

X is- $(CH_2)_n$-; $-CH(R^2)(CH_2)_n$-; $-CH_2O(CH_2)_n$-; $-CH_2NH$-; benzyl, $-C(R^2)=CH$-; $-CH_2CH(OH)$-; or thiazol-2,5-diyl;

Y is –S-S-; $-(CH_2)_n$-; -O-; -NH-; $-N(R^2)$-; -CH=CH-; -NHC(O)NH-;- $N(R^2)C(O)N(R^2)$-; $-N[CH_2C_6H_3(OCH_3)_2]$-; $-N(CH_2C_6H_5)$-; $-N(CH_2C_6H_5)C(O)N(CH_2C_6H_5)$-; -N(alkoxyalkyl)-; N(cycloalkyl-methyl)-; 2,6-pyridyl; 2,5-furanyl; 2,5-thienyl; 1,2-cyclohexyl; 1,3-cyclohexyl; 1,4-cyclohexyl; 1,2-naphthyl; 1,4-naphthyl; 1,5-naphthyl; 1,6-naphthyl; biphenylen; or 1,2-phenylen,1,3-phenylen and 1,4-phenylen, wherein the phenylen groups are optionally substituted by 1 – 4 substituents, selected from halogen, lower

alkyl, lower alkoxy, hydroxy, carboxy, -COO-lower alkyl, nitrilo, 5-tetrazol, (2-carboxylic acid pyrrolidin-1-yl)-2-oxo-ethoxy, N-hydroxycarbamimidoyl, 5-oxo[1,2,4]oxadiazolyl, 2-oxo-[1,2,3,5]oxathiadiazolyl, 5-thioxo[1,2,4]oxadiazolyl and 5-tert-butylsulfanyl-[1,2,4]oxadiazolyl;

X' is $-(CH_2)_n-$; $-(CH_2)_nCH(R^2)-$; $-(CH_2)_nOCH_2-$; $-NHCH_2-$; benzyl, $-CH=C(R^2)-$; $-CH(OH)CH_2$; or thiazol-2,5-diyl;

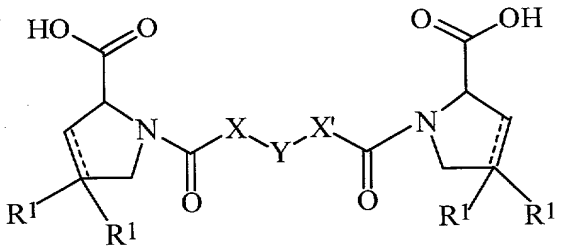
R^2 is lower alkyl, lower alkoxy or benzyl and

n is 0-3,

or a pharmaceutically acceptable salt or mono- or diester thereof.

6. Agent according to claim 1, wherein each ligand is selected to be specific for an individual target protein, and to be bound by the protein with a dissociation constant which is no more than 1 millimolar.

7. Agent for the depletion of an unwanted protein population from the plasma of a subject, which agent comprises a plurality of ligands covalently co-linked so as to form a complex with a plurality of the proteins in the presence thereof, wherein at least two of the ligands are the same or different and are capable of being bound by ligand binding sites present on one or more proteins selected from a normal or abnormal, variant, protein of any of the following types: cytokine, lipoprotein, autoantibody, acute phase protein, amyloidogenic protein, complement protein, or coagulation protein, wherein the agent is a non-proteinaceous agent other than a D-proline of the formula



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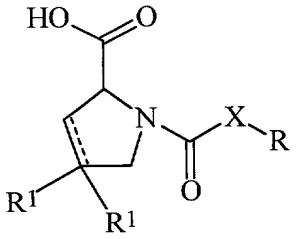
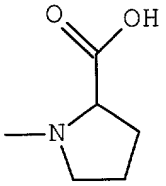


I-A I-B

wherein

R is



the group ;

R^1 is hydrogen or halogen;

X is- $(CH_2)_n$-; -$CH(R^2)(CH_2)_n$-; -$CH_2O(CH_2)_n$-; -CH_2NH-; benzyl, -$C(R^2)$=CH-; -$CH_2CH(OH)$-; or thiazol-2,5-diyl;

Y is –S-S-; -$(CH_2)_n$-; -O-; -NH-; -$N(R^2)$-; -CH=CH-; -NHC(O)NH-;- $N(R^2)C(O)N(R^2)$-; -$N[CH_2C_6H_3(OCH_3)_2]$-; -$N(CH_2C_6H_5)$-; -$N(CH_2C_6H_5)C(O)N(CH_2C_6H_5)$-; -N(alkoxyalkyl)-; N(cycloalkyl-methyl)-; 2,6-pyridyl; 2,5-furanyl; 2,5-thienyl; 1,2-cyclohexyl; 1,3-cyclohexyl; 1,4-cyclohexyl; 1,2-naphthyl; 1,4-naphthyl; 1,5-naphthyl; 1,6-naphthyl; biphenylen; or 1,2-phenylen,1,3-phenylen and 1,4-phenylen, wherein the phenylen groups are optionally substituted by 1 – 4 substituents, selected from halogen, lower alkyl, lower alkoxy, hydroxy, carboxy, -COO-lower alkyl, nitrilo, 5-tetrazol, (2-carboxylic acid pyrrolidin-1-yl)-2-oxo-ethoxy, N-hydroxycarbamimidoyl, 5-oxo[1,2,4]oxadiazolyl, 2-oxo-

[1,2,3,5]oxathiadiazolyl, 5-thioxo[1,2,4]oxadiazolyl and 5-tert-butylsulfanyl-[1,2,4]oxadiazolyl;

X' is $-(CH_2)_n-$; $-(CH_2)_nCH(R^2)-$; $-(CH_2)_nOCH_2-$; $-NHCH_2-$; benzyl, $-CH=C(R^2)-$; $-CH(OH)CH_2$; or thiazol-2,5-diyl;

R^2 is lower alkyl, lower alkoxy or benzyl and

n is 0-3,

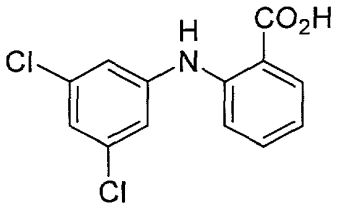
or a pharmaceutically acceptable salt or mono- or diester thereof.

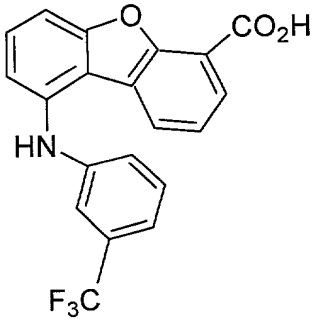
8. Agent according to claim 7, wherein the ligand binding site is from an acute phase protein comprising SAA.

9. Agent according to claim 7, wherein the ligand binding site is from serum amyloid P component (SAP).

10. Agent according to claim 8, wherein the ligand binding site is from an amyloidogenic protein comprising a monoclonal immunoglobulin light chain, transthyretin, β_2-microglobulin or lysozyme.

11. Agent according to claim 10, wherein the ligand binding site is from transthyretin and at least one of the ligands comprises





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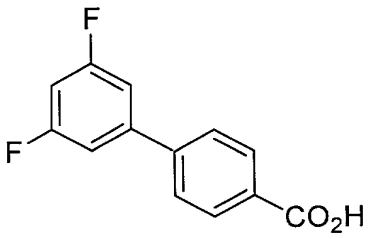


12. Agent according to claim 10, wherein the ligand binding site is from lysozyme and at least one of the ligands comprises a disaccharide or oligosaccharide analogue containing at least N-acetyl muramic acid linked via its C1 atom to the C4 atom of, for example, N-acetyl glucosamine, with the O atom of the 1,4 β glycosidic linkage replaced by a carbon or other non-O atom.

13. Agent according to claim 7, wherein the ligand binding site is from an autoantibody and at least one of the ligands comprises an epitope to which the autoantibody is specific.

14. Agent according to claim 1 wherein each ligand is capable of binding to the same ligand binding site.

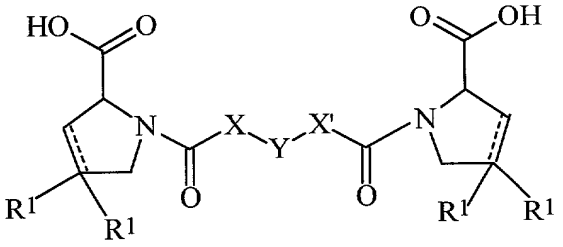
15. Agent according to claim 1, wherein at least two ligands are different from one another and are capable of being bound by different proteins.

16. Agent according to claim 15, wherein one of the ligands is capable of being bound by SAP.

17. Pharmaceutical composition for the depletion of an unwanted protein population from the plasma of a subject, which comprises an agent acording to claim 1 and a pharmaceutically-acceptable excipient, diluent or carrier.

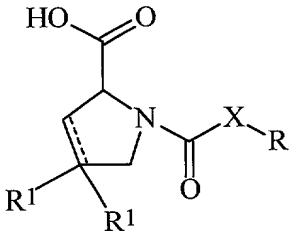
18 Method for the depletion of an unwanted protein population from the plasma of a subject, which comprises administering to the subject a therapeutically effective amount of a non-proteinaceous agent, which agent comprises a plurality of ligands covalently co-linked so as to form a complex with a plurality of the proteins in the presence thereof, wherein at least two of the ligands are the same or different and are capable of being bound by ligand binding sites present on the proteins.

19. Method according to claim 18, wherein the agent is a D-proline of the formula



I-A

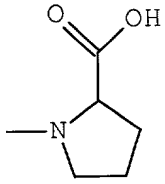
or



I-B

wherein

R is



the group ;

R^1 is hydrogen or halogen;

X is- $(CH_2)_n$-; -$CH(R^2)(CH_2)_n$-; -$CH_2O(CH_2)_n$-; -CH_2NH-;
benzyl, -$C(R^2)$=CH-; -$CH_2CH(OH)$-; or thiazol-2,5-diyl;

Y is –S-S-; -$(CH_2)_n$-; -O-; -NH-; -$N(R^2)$-; -CH=CH-; -NHC(O)NH-;-
$N(R^2)C(O)N(R^2)$-; -$N[CH_2C_6H_3(OCH_3)_2]$-; -$N(CH_2C_6H_5)$-;
-$N(CH_2C_6H_5)C(O)N(CH_2C_6H_5)$-; -N(alkoxyalkyl)-;
N(cycloalkyl-methyl)-; 2,6-pyridyl; 2,5-furanyl; 2,5-thienyl; 1,2-cyclohexyl; 1,3-cyclohexyl; 1,4-
cyclohexyl; 1,2-naphthyl; 1,4-naphthyl; 1,5-naphthyl; 1,6-naphthyl;
biphenylen; or 1,2-phenylen,1,3-phenylen and 1,4-phenylen, wherein the phenylen groups are optionally substituted by 1 – 4 substituents, selected from halogen, lower alkyl, lower alkoxy, hydroxy, carboxy, -COO-lower alkyl, nitrilo, 5-tetrazol, (2-carboxylic acid pyrrolidin-1-yl)-2-oxo-ethoxy, N-hydroxycarbamimidoyl, 5-oxo[1,2,4]oxadiazolyl, 2-oxo-[1,2,3,5]oxathiadiazolyl, 5-thioxo[1,2,4]oxadiazolyl and 5-tert-butylsulfanyl-[1,2,4]oxadiazolyl;

X' is –$(CH_2)_n$-; -$(CH_2)_nCH(R^2)$-; -$(CH_2)_nOCH_2$-; -$NHCH_2$-;
benzyl, -$CH=C(R^2)$-; -$CH(OH)CH_2$; or thiazol-2,5-diyl;

R^2 is lower alkyl, lower alkoxy or benzyl and

n is 0-3,

or a pharmaceutically acceptable salt or mono- or diester thereof.

20. Method according to claim 19, wherein the D-proline is (R)-1-[6-(R)-2-Carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid or a pharmaceutically acceptable salt or mono- or diester thereof.

21. Method according to claim 18, wherein the ligands are covalently co-linked in the agent by a linker.

22. Method according to claim 21, wherein the linker comprises a linear or branched hydrocarbylene in which one or more of the carbon atoms thereof is optionally substituted by a heteroatom.

23. Method according to claim 18, wherein the agent has two ligands.

24. Method for the depletion of an unwanted protein population from the plasma of a subject, which comprises administering to the subject a therapeutically effective amount of a non-proteinaceous agent, which agent has the general structure Ligand-linker-Ligand and is capable of forming a complex with a plurality of the proteins in the presence thereof, wherein the ligands are the same or different and are capable of being bound by ligand binding sites present on the proteins.

25. Method according to claim 18, wherein each ligand in the agent is selected to be specific for an individual target protein, and to be bound by the protein with a dissociation constant which is no more than 1 millimolar.

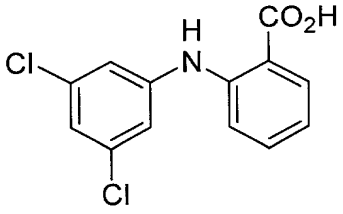
26. Method for the depletion of an unwanted protein population from the plasma of a subject, which comprises administering to the subject a therapeutically effective amount of a non-proteinaceous agent, which agent comprises a plurality of ligands covalently co-linked so as to form a complex with a plurality of the proteins in the presence thereof, wherein at least two of the ligands are the same or different and are capable of being bound by ligand binding sites present on one or more proteins selected from a normal or abnormal, variant, protein of any of the following types: cytokine, lipoprotein, autoantibody, acute phase protein, amyloidogenic protein, complement protein, or coagulation protein.

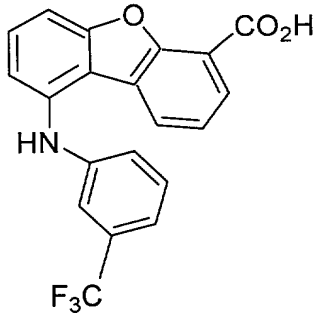
27. Method according to claim 26, wherein the ligand binding site is from an acute phase protein comprising SAA.

28. Method according to claim 26, wherein the ligand binding site is from serum amyloid P component (SAP).

29. Method according to claim 27, wherein the ligand binding site is from an amyloidogenic protein comprising a monoclonal immunoglobulin light chain, transthyretin, β_2-microglobulin or lysozyme.

30. Method according to claim 29, wherein the ligand binding site is from transthyretin and at least one of the ligands comprises





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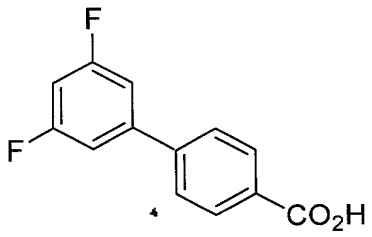

31. Method according to claim 29, wherein the ligand binding site is from lysozyme and at least one of the ligands comprises a disaccharide or oligosaccharide analogue containing at least N-acetyl muramic acid linked via its C1 atom to the C4 atom of, for example, N-acetyl glucosamine, with the O atom of the 1,4 β glycosidic linkage replaced by a carbon or other non-O atom.

32. Method according to claim 26, wherein the ligand binding site is from an autoantibody and at least one of the ligands comprises an epitope to which the autoantibody is specific.

33. Method according to claim 18 wherein each ligand of the agent is capable of binding to the same ligand binding site.

34. Method according to claim 18, wherein at least two ligands of the agent are different from one another and are capable of being bound by different proteins.

35. Method according to claim 34, wherein one of the ligands of the agent is capable of being bound by SAP.